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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/933,115	08/20/2001	Paul B. Fisher	A34466 (070050.1618)	7088

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
09/12/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/933,115	FISHER, PAUL B.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 8/7/07.

The amendment filed 8/7/07 is acknowledged and has been entered.

Claim 81 is currently pending in the application and is addressed herein.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 81 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In this case, the claims encompass a method of treating a subject having pancreatic cancer associated with a *ras* mutation causing increased *RAS* activity by administering a combination of a nucleic acid encoding SEQ ID NO: 2 and an antisense *ras* oligonucleotide. It is noted the specification explicitly indicates:

> "The term 'RAS' as used herein refers to members of the RAS family of proteins, including the proteins human H-RAS, K-RAS, and N-RAS and the corresponding genes *H-ras, K-ras and N-ras*... "(See page 26, paragraph [0056]).

Therefore, the claim encompasses method of treating a subject having pancreatic cancer associated with ANY *ras* mutation (such as a K-*ras*, H-*ras,* N-*ras,* or any other *ras* family member) causing increased *RAS* activity by administering a combination of a nucleic acid encoding SEQ ID NO: 2 and any antisense *ras* oligonucleotide (i.e., not necessarily a K-*ras* antisense oligonucleotide).

Therefore, the claims encompass treating a subject having pancreatic cancer that is associated with any of a large genus of *ras* molecules using an antisense *ras* oligonucleotide. As such the claims encompass a genus comprising a large number of different *ras* molecules and antisense *ras* oligonucleotides.

As indicated above, the specification has only identified three *ras* family members, K-*ras,* H-*ras* and N-*ras*, but the specification also discloses that an activating mutation of the K-*ras* oncogene has been associated with pancreatic cancer (e.g., see page 5). However, the specification does not appear to disclose whether or not any other *ras* other than K-*ras* is associated with pancreatic cancer.

Looking to the prior art for guidance, it appears that only the activating mutations of K-*ras* has been associated with pancreatic cancer. For instance, see Mulligan et al. (Hum Pathol 30:602-610, 1999) and Bos (Cancer Research 49:4682-4689, 1989) both appear to indicate that although K-*ras* mutations have been associated with pancreatic cancer, H-*ras* and N-*ras* have not. Specifically, Mulligan teaches "The possibility that mutation of overexpression of N or H p21*ras* results in the accumulation of the active forms of these proteins in K-*ras* mutation-

negative cases appears unlikely given these findings" (see page 609, first column). Also, Bos teaches that although H-*ras*, K-*ras* and N-*ras* mutations are recognized as oncogenes associated with various types of tumors, only the K-*ras* mutation was identified in pancreatic tumor cells (e.g., see Table 1, page 4683).

Therefore, in view of the limited disclosure regarding the *ras* mutations which increase *RAS* activity in pancreatic cancer cells, and in view of the fact that non-K-*ras* mutations are not recognized in the art as being associated pancreatic cancer, the specification does not provide adequate written description of the genus of *ras* mutations encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only mutations of K-*ras* meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written

description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

3. Claim 81 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method of treating a subject having pancreatic cancer associated with a K-*ras* mutation causing increased K-*RAS* activity, comprising administering, to the subject (a) a viral vector comprising a nucleic acid encoding a protein having SEQ ID NO: 2, in expressible form, and (b) an antisense K-*ras* oligonucleotide, in amounts which are effective, in combination, in (i) increasing the amount of the differentiation associated protein, *MDA-7* and (ii) decreasing K-*RAS* activity in cells of the pancreatic cancer, wherein the viral vector and the antisense K-*ras* oligonucleotide are administered to the subject by a method selected from the group consisting of intra-tumor injection and instillation following surgical resection of a tumor into the tumor bed;

does not reasonably provide enablement for treating a subject having pancreatic cancer associated with a *ras* mutation other than K-*ras* using a non-K-*ras* antisense oligonucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The invention is drawn to a method of treating pancreatic cancer using a combination of gene therapy and antisense therapy.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

As indicated above, the claims encompass a method of treating a subject having pancreatic cancer associated with a *ras* mutation causing increased *RAS* activity by administering a combination of a nucleic acid encoding SEQ ID NO: 2 and an antisense *ras* oligonucleotide. It is noted the specification explicitly indicates:

> "The term 'RAS' as used herein refers to members of the RAS family of proteins, including the proteins human H-RAS, K-RAS, and N-RAS and the corresponding genes *H-ras, K-ras and N-ras...* "(See page 26, paragraph [0056]).

Therefore, the claim encompasses method of treating a subject having pancreatic cancer associated with ANY *ras* mutation (such as a K-*ras*, H-*ras,* N-*ras,* or any other *ras* family member) causing increased *RAS* activity by administering a combination of a nucleic acid encoding SEQ ID NO: 2 and any antisense *ras* oligonucleotide (i.e., not necessarily a K-*ras* antisense oligonucleotide).

The unpredictability of the art and the state of the prior art

The prior art only appears to recognize K-*ras* mutations as being associated with increased *RAS* activity in pancreatic cancer cells.

For instance, see Mulligan et al. (Hum Pathol 30:602-610, 1999) and Bos (Cancer Research 49:4682-4689, 1989) both appear to indicate that although K-*ras* mutations have been associated with pancreatic cancer, H-*ras* and N-*ras* have not. Specifically, Mulligan teaches "The possibility that mutation of overexpression of N or H p21*ras* results in the accumulation of the active forms of these proteins in K-*ras* mutation-negative cases appears unlikely given these findings" (see page 609, first column). Also, Bos teaches that although H-*ras*, K-*ras* and N-*ras* mutations are recognized as oncogenes associated with various types of tumors, only the K-*ras* mutation was identified in pancreatic tumor cells (e.g., see Table 1, page 4683).

Working Examples and Guidance in the Specification

The specification does not appear to indicate that any other mutant *ras* molecule is associated with increased *RAS* activity in pancreatic cancer. Furthermore, the only examples provided utilize antisense oligonucleotides that inhibit K-*ras* expression and activity.

Quantity of Experimentation

Considering that the prior art does not recognize non-K-*ras* mutations with pancreatic cancer, and considering the teaching of Mulligan et al. that, "The possibility that mutation of overexpression of N or H p21*ras* results in the accumulation of the active forms of these proteins in K-*ras* mutation-negative cases appears unlikely given these findings" (see page 609, first column), additional experimentation would be required before the broadly claimed method could be predictably practiced. For instance, a great deal of experimentation would be required in

order to associate non-K-*ras* mutations with pancreatic cancer, considering that others have tried but have not successfully demonstrated that other *ras* mutations increase *RAS* activity in pancreatic cancer (e.g., see Mulligan et al. and Bos cited above). Furthermore, additional experimentation would be required to show that a *ras* antisense molecule which inhibits the expression of a *ras* molecule other than K-*ras,* would be effective in the claimed method of treating pancreatic cancer. Considering that no other *ras* molecule has been associated with pancreatic cancer, it is expected that the additional experimentation would be enormous. The additional experimentation would amount to trial-and-error testing with no guarantee of success.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the full scope encompassed by instant claims. Therefore, additional experimentation is required before one of skill in the art could make and use the claimed invention to its full scope. The amount of additional experimentation required to perform the broadly claimed invention is undue.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner
Art Unit 1635